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|---|---|
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| ART UNIT | PAPER NUMBER |
| 1652 | 9 |

DATE MAILED: 01/14/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/518,081 | SHAPIRO, LELAND | |
| | Examiner | Art Unit | |
| | Kathleen M Kerr | 1652 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *23 November 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) *26-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *2* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

## DETAILED ACTION

### *Application Status*

1. The instant Office action is in response to Applicants' election of invention and species to be examined (see below). Claims 1-28 are pending in the instant application.

### *Election*

2. In Paper No. 4, the pending claims were restricted into two inventions, Group I = Claims 1-25 and Group II = Claims 26-28 with a required election of species for Group I. In Paper No. 5, Applicants elected Group I, Claims 1-25 with traverse; however, no election of species was made, and the response was held to be non-responsive in Paper No. 6. In Paper No. 7, Applicants elected, with traverse, the species of $\alpha_1$-antitrypsin of the invention of Group I to be examined.

Applicant's election with traverse of Group I in Paper No. 5 is acknowledged. The traversal is on the ground(s) that "a search and examination of all the claims would not impose a serious search burden to prosecute all of the claims (and all of the species) of the application. This is not found persuasive because the searches for the two groups (inventions) are wholly different with one group based on disease and another based on antitrypsin activity. This distinct search is evident in the different class/subclass classifications noted in Paper No. 4. This argument is also not found persuasive as related to the species election because the searches are divergent when drawn to different serine protease inhibitors.

The requirement is still deemed proper and is therefore made FINAL. Claims 1-25 will be examined herein as drawn to the elected species that is where the serine protease inhibitor is $\alpha_1$-antitrypsin.

***Priority***

3. The instant application is granted the benefit of priority for the U.S. Provisional Application No. 60/123,167 filed on March 5, 1999 as requested in the declaration and the first lines of the specification.

***Information Disclosure Statement***

4. The information disclosure statement filed on June 19, 2000 (Paper No. 2) has been reviewed, and its references have been considered as shown by the Examiner's initials next to each citation on the attached copy.

5. The information disclosure statement filed on May 4, 2001 (Paper No. 3) cannot be reviewed without submission of all the noted references for this particular application; submission in related cases is insufficient. Moreover, the cited documents must be pertinent to the patentability of the claims pending in the **instant** application.

***Objections to the Specification***

6. In the specification, the Title is objected to for not completely describing the claimed subject matter. The Examiner suggests the addition of ---Using Serine Protease Inhibitors--- to the title for completeness.

### *Objections to the Claims*

7. Claims 8 and 25 are objected to because of the following informalities, which will be defined in Claim 8 and are identical in Claim 25:

a) None of the drugs in the long list should be capitalized as proper names since they are all the general, chemical name.

b) On page 21, line 12, the "and" should be deleted.

c) Throughout the list (such as on page 21, line 14), "benzyloxycarbonyl", when first in the chemical name, should have parentheses (both open and closed) surrounding it as written in the first drug, "(benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide" (added underlining for emphasis)

d) On page 21, line 115, the comma after "prolinamide" should be a semicolon.

e) On page 25, line 3, the "and" should be deleted since the salts and combinations are the last members of the Markush group.

f) The Examiner suggests listing the numerous drugs one per line (or lines) for ease of reading and to prevent typographical errors as noted above.

Appropriate correction is required.

### *Claim Rejections - 35 U.S.C. § 112*

8. The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1-18 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "excessive apoptosis", as found in Claim 1, line 4, and in Claim 18, line 2, is a relative term that is not defined in either the specification or the art so that one of skill in the art would understand the metes and bound of the instant claims.

10. Claims 3, 4, and 22 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following phrases are unclear:

α1-antitrypsin-like agent
variant of α1-antitrypsin
anticathepsin G agent
antitryptase TL2-agent
antifactor Xa agent
antielastase agent
antiproteinase-3 agent

These groups are all claimed as genera; the article "an" preceding each indicates more than one compound in each member of the Markush group. It is unclear if compounds are exclusively in one of these groups or whether generic compounds can be in all of them. The specific activity of these compounds is unclear – Is human trypsin inhibited? Must all trypsins be inhibited? And most particularly, the definition of α1-antitrypsin-like and variant of α1-antitrypsin are wholly unclear. Appropriate definition is required of all these terms.

11. Claims 4, 9, 12-14, 16, and 24 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "about" is unclear in the extent to which this

adjective allows for error in the measurement – Is "about" indicative of +/-10%? 15%? Thus, the metes and bounds are unclear.

12. Claims 8 and 25 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The abbreviation "BTD" in Claim 8, page 22, line 29 and in Claim 25, page 28, line 24 is unclear as to its meaning.

13. Claim 15 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "buccally" is unclear. Appropriate citation of a definition in the art is required.

14. Claim 18 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "exhibiting mammalian α1-antitrypsin or α1-antitrypsin-like activity" does not clearly define what compounds should be used. The level of inhibitory activity is undefined. Additionally, particular mammalian activities are different among different species. Appropriate clarification is required.

15. Claim 24 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is unclear how blood concentrations are related to inhibitor concentrations in a cell. The parent claim 21 is not drawn to treating a subject, but to treating a cell. It would be

unreasonable to extend the scope of Claim 21 to that of treating a subject; no enablement rejection has been set forth for such an interpretation.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

16. Claims 1-18 are rejected under 35 U.S.C. § 112, first paragraph, enablement, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The instant claims are drawn to methods of treating diseases, characterized by apoptosis, using serine protease inhibitors. One of skill in the art would be required to perform undue experimentation to practice the claimed methods to the full extent of their scope due to the cause vs. effect nature of disease and apoptosis in general.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered

in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

While a general link between apoptosis and particular diseases, such as those listed in the specification and in Claim 11, has been identified in the art, this link is very vague as to its nature. For example, apoptosis inhibitors are not clearly set forth in the art as cancer treatments because of the complex and pervasive nature of apoptosis in patients. Apoptosis is defined as organized cell death that comes about via a mass and variety of different reactions. It is unclear where in any disease cycle apoptosis becomes a significant factor in the propagation of the disease and which cascade(s) of events are involved. Thus the treatment of apoptosis as the treatment of diseases linked to apoptosis skips numerous intermediate steps of connection between the diseases and apoptosis inhibitors. The examples in the specification for the use of serine protease inhibitors to inhibit apoptosis are as follows:

1) stroke and myocardial infarction in rats *in vivo* (no data shown),
2) mouse cells in culture where α1-antitrypsin effects TNF-induced apoptosis (no data shown),
3 and 4) suggested co-administration of serine protease inhibitors (no specific example of data),
5) rat cells in culture where α1-antitrypsin and CE-2072 reduce serum-depletion-induced apoptosis (data in Figure 2),
6) treating donor kidneys with α1-antitrypsin (no data shown),
7) variants of α1-antitrypsin in example 1 (no data shown), and
8) rat cells in culture where α1-antitrypsin "completely reverses" serum-depletion-induced apoptosis (no data shown),

which examples show **no** indication of effective disease treatment and **little** data identifying the inhibition of even apoptosis, particularly for the large genus that is serine protease inhibitors. The only example with any data uses two serine protease inhibitors, α1-antitrypsin and CE-2072, on cultured cells induced to apoptosis via serum-depletion-induced. Serum-depletion-induced apoptosis has not been described as correlating to the apoptosis of particular disease states. Thus, the link between the data of these experiments and disease states is wholly lacking. It is wholly unclear how these specific cultured cells experiments enables the treatment of any disease linked to apoptosis, not only because the links between apoptosis and particular diseases are unclear but also because of the lack of *in vivo* experimentation. The art is wholly unpredictable for using apoptosis inhibitors for treating even specific diseases states, let alone any disease characterized by some amount of apoptosis.

17. Claims 6 and 23 are rejected under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being possibly being enabling for using derivatized serine protease inhibitors that retain the inhibitory activity, does not reasonably provide enablement for derivatized serine protease inhibitors that no longer function to inhibit serine proteases. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. To practice the above methods with derivatized compounds that no longer inhibit serine proteases would require undue experimentation of one of skill in the art.

The factors to be considered in determining whether undue experimentation is required are summarized.

The specification provides no guidance or working examples of using inhibitors other than effective serine protease inhibitors. One of skill in the art would be required to test anew the derivatized compounds for some new activity that would be wholly unpredictable from its former activity as a serine protease inhibitor. Thus, the instant claims are not enabled to the full extent of their scope.

18. Claims 19-20 are rejected under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for *reducing* apoptosis in cell or tissue culture, does not reasonably provide enablement for *inhibiting* apoptosis in cell or tissue culture or even reducing apoptosis in a mammalian organ. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. The Examiner notes that the full scope of Claim 20 lacks enablement. To reduce apoptosis in a mammalian organ or wholly inhibit apoptosis in cell or tissue culture would require undue experimentation of one of skill in the art.

The factors to be considered in determining whether undue experimentation is required are summarized. The experiments set forth in the specification are also summarized above.

The specification provides no working examples of entire inhibition of apoptosis in any experiment. The ability to wholly inhibit such a broadly invasive set of reactions is wholly unpredictable. The specification provides no working examples of treating whole organs effectively. The ability to pervade such an organ, particularly one awaiting transplant, has not been effectively demonstrated. Moreover, the effectiveness of serine proteases to inhibit various progressions of apoptosis in whole organs has in no way been demonstrated and is wholly unpredictable. The specification provides guidance but no explanation of any reasonable

expectation of success of such experiments. The art is also lacking in this arena. As such, the instant claims are not enabled to the full extent of their claimed scope.

19. Claims 21-25 are rejected under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for using certain serine protease inhibitors to inhibit some forms of apoptosis, does not reasonably provide enablement for using *all* serine protease inhibitors to inhibit *all* forms of apoptosis. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized. The experiments set forth in the specification are also summarized above. The Examiner also noted that TNF-induced apoptosis is inhibited by α1-antitrpysin (see art rejection below).

The breadth of the instant claims reaches to all forms of apoptosis wherein the examples provided are specific to an experimental set of apoptotic circumstances and inhibitors. The reactions of apoptosis are complex and broad and mostly poorly understood; the cascading events make "control" or "inhibition" mechanisms difficult to interpret. The simple experiments provided in the instant specification do not enable the broad-brush use of all serine protease inhibitors against apoptosis because the effects are not reasonably understood. Particularly, the effects of the long list of serine protease inhibitors of Claim 25 on apoptosis cannot be predicted with any surety. Moreover, the effects of all serine protease inhibitors cannot be predicted to effect all induced forms of apoptosis since no mechanisms of the effects demonstrated in the

specification are clear or predictable. When complex reactions, such as apoptosis, are to be controlled, numerous experimental controls and variously induced forms of apoptosis should be evaluated to affect some predictability. This is not the case in the instant specification. Thus, without predictability and in view of the enormous breadth of the instant claims, they are not enabled to the full extent of their scope.

### *Claim Rejections - 35 U.S.C. § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

20. Claims 21-22 are rejected under 35 U.S.C. § 102(b) as being anticipated by van Molle *et al.* The instant claims are drawn to methods of inhibiting apoptosis using α1-antitrypsin.

van Molle *et al.* teach the inhibition of TNF-induced apoptosis using α1-antitrypsin (see title, for example) in mouse hepatocytes.

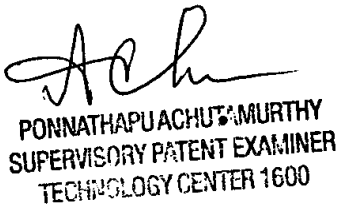
### *Conclusion*

21. Claims 1-25 are not allowed for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathleen M Kerr whose telephone number is (703) 305-1229. The examiner can normally be reached on Monday through Friday, from 8:30am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathupura Achutamurthy can be reached on (703) 308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-0294 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

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